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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,474	04/12/2006	Hiroko Kojima	062405	3422

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EXAMINER	
SHEN, WU CHENG WINSTON	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
12/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,474	KOJIMA ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-12 and 14-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-12 and 14-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 10/14/2008 has been entered. Claims 1-8 and 13 are cancelled. Claims 9-12 and 14-23 are pending. Claims 9-12 and 17-20 are amended. Claims 9-12 and 14-23 are currently under examination.

The Declaration filed by Hiroko Kojima under 37 C.F.R. § 132 on 10/14/2008, has been considered.

This application 10/575,474 filed on 04/12/2006 is a 371 of PCT/JP04/15673 filed on 10/15/2004 and claims the priority of foreign application JAPAN 2003-355505 filed on 10/15/2003.

Claim Objections

1. Previous objection of claims 9 and 17 because of the following informalities: (i) claims 9 and 17 recites the phrase "osteo-inducible transcription factor Cbfa1", and (ii) claims 9 and 17 recites the phrase "vector carrying a gene encoding", is ***withdrawn*** because the claims have been amended.

Claims 9 and 17 have been amended to recite the phrases "osteo-inducing transcription factor Cbfa1" and "vector comprising a gene encoding".

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claims 9-12 and 14-23 are newly rejected under 35 U.S.C. 102(e) and under 35 U.S.C. 102(a) as being anticipated by **Doll et al.** (Doll et al., U.S Patent application Publication 2003/0235564, Publication date, Dec. 25, 2003, filed on May 13, 2003) as evidenced by **Ogawa et al.** (US patent 5,030,611, issued 07/09/1991). Applicant's arguments filed 10/14/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 4-8 of the office action mailed on 06/20/2008.

For clarity and completeness of this office action, the reasons of record advanced on pages 4-8 of the office action mailed on 06/20/2008, is revised below to address claim amendments.

Independent claims 9 and 17 are directed to a bioadaptable porous material on which an adenoviral or retroviral vector carrying a gene encoding an osteo-inducing transcription factor Cbfa1 is adsorbed, wherein the bioadaptable porous material is any member selected from the group consisting of α-TCP, β-TCP (tricalcium phosphate), collagen, polylactic acid, hyaluronic acid, polyglycolic acid, and a complex of any thereof. Dependent claims recite limitation further comprising bone marrow derived cells that are osteoblasts.

Claim interpretation: Bone marrow derived cells, including osteoblasts, recited in claims 14-16 and 21-23 read on bone marrow derived cells that are not transfected, and bone marrow

derived cells that are transfected with any viral vector encoding any gene of interest. In other words, claims 14-16 and 21-23 read on addition of non-recombinant bone marrow derived cells to the implant as well as bone marrow derived cells that are transformed with the gene recited in claim 9. The limitation "an individual in need of said implant" recited in claims 16 and 23 reads on any individual.

With regard to Cbfa1 recited in independent claims 9 and 17 of instant application, Doll et al. teaches transcription factor Runx2, also referred to as Cbfa1 (core binding factor alpha 1) and as Osf2 (osteoblast specific factor 2), which is a regulator of osteoblast differentiation (See paragraph [0022], column 3, Doll et al. 2003).

Doll et al. teach a pharmaceutical composition comprising in combination the Runx2 protein, a polynucleotide encoding the Runx2 protein, or a cell that has been transformed with a polynucleotide encoding Runx2 protein, in a pharmaceutically acceptable carrier (which includes water, buffer, saline etc), the carrier comprising a bio-compatible, biodegradable polymeric matrix. Another aspect of the invention includes a device comprising the above-described pharmaceutical composition in combination with a sterile and substantially antigen-free, pre-shaped allograft or xenograft bone implant (See abstract, Doll et al., 2003).

With regard to an implant consisting of a bioadaptable material and its association with DNA (claims 9-12 and 17-20 of instant application), Doll et al. teach a method for repairing a bone defect comprising administering to a mammalian patient at the site in need of treatment a pharmaceutical composition, comprising in combination the Runx2 protein, a polynucleotide encoding the Runx2 protein, or a cell that has been transformed with *a polynucleotide encoding*

Runx2 protein, in a pharmaceutically acceptable carrier wherein the carrier is a bio-compatible, biodegradable polymeric matrix (See abstract, Doll et al., 2003). Doll et al. teach viral vectors have higher transaction (ability to introduce genes) abilities than do most chemical or physical methods to introduce genes into cells. And the viral vectors include retroviral vectors and adenoviral vectors (See paragraphs [0096], [0097], and [0098], Doll et al., 2003).

With regard to β-TCP (β-tricalcium phosphate) (claims 10-12 and 17-20 of instant application), Doll et al. teach the reports on the use of β-tricalcium phosphate for implantation; and reports on the use of demineralized bone implants (See paragraphs [0053], column 7, Doll et al., 2003).

The inherent properties of β-TCP to adsorb nucleic acids and/or proteins are known in the art. For instance, Ogawa et al. teaches packing tricalcium phosphate (TCP) or hydroxyapatite for chromatography, and TCP exhibits a high ability to adsorb acidic proteins, in the context of separating and purifying various biomaterials such as proteins, enzyme, nucleic acid acids, etc. (See for instance, lines 54-59, 28-33, column 4, Ogawa et al., 1991).

With regard to the implant further comprising bone marrow derived cells such as osteoblasts (claims 14-16 and 21-23 of instant application), Doll et al. teaches examples for bone repair and/or treatment of osteoporosis uses osteocytes/osteoblasts transfected with bone growth factor genes (See paragraph [0115], Doll et al., 2003). Doll et al. further teaches combination of a form of Runx2 with a delivery system (which reads on a cell such as osteoblasts) that comprises biologically active molecule, which enhances the rate of bone repair (See paragraph [0116], Doll et al., 2003).

With regard to nucleic acid (i.e. claimed retroviral vector) been absorbed by β-TCP, the following citations, in addition to the disclosure of Ogawa et al., further support the inherent properties of β-TCP anticipate the adsorption of nucleic acids.

"Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product (In re Ludtke). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972))."

"When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433. See also Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), In re Ludtke, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), Northam Warren Corp. v. D. F. Newfield Co., 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934.) See MPEP 2113 and MPEP 2112.01.
Even though product-by-process claims are limited by and defined by the process; determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

"The Patent Office bears a lesser burden of proof in making out a case of prima facie obviousness for product-by-process claims because of their peculiar nature" than when a product

is claimed in the conventional fashion. In re Fessmann, 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983).

Thus, Doll et al. clearly anticipates claims 9-12 and 14-23 of instant invention.

Applicant's arguments

Applicant argues that Ogawa did disclose the adsorption of nucleic acids onto biomaterials in addition to adsorption of acidic proteins onto biomaterials; such alleged adsorption would not be an inherent property of hydroxyapatite or 13- TCP. Rather, Applicant argues that the adsorption is dependent on the manner in which the ceramics material is produced. Applicant argues that, for example, Ogawa identifies another method of producing hydroxyapatite, in which "disadvantageously the ability of the treated particles to adsorb acidic proteins such as bovine serum albumin (BSA) is lowered." Column 1, lines 52-54. As such, even if, *arguendo*, Ogawa disclosed or suggested adsorption of nucleic acids onto a bioadaptable material, it can be presumed that such adsorption would also depend on the method of manufacture of the bioadaptable material (See pages 7-8 of Applicant's remark filed on 10/14/2008). Accordingly, Applicant argues that, in order to rely on the argument that Doll inherently discloses the claimed subject matter, it must be shown that adsorption of a vector comprising the Cbfa1 gene onto the bioadaptable material of Doll necessarily occurs. As explained above, adsorption of biomaterials does not necessarily occur in a bioadaptable material

made of hydroxyapatite or tricalcium phosphate. Rather, the ability of a bioadaptable material made of hydroxyapatite or tricalcium phosphate to adsorb biomaterials is at least partially dependent on its method of manufacture (See page 8 of Applicant's remark filed on 10/14/2008)

Applicant argues that, furthermore, even if, *arguendo*, Ogawa suggested the affinity of 13-TCP to proteins and nucleic acids, it is difficult for proteins or nucleic acids to be efficiently adsorbed to a porous 13-TCP by the method described in Doll, irrespective of the method of manufacture of the bioadaptable porous materials. The adsorption efficacy of 13-TCP to proteins or nucleic acids is very low when β-TCP is merely mixed with a solution comprising proteins or nucleic acids (See page 9 of Applicant's remark filed on 10/14/2008). Accordingly, Applicant argues that the ability of the bioadaptable material to adsorb a biomaterial is not only based on the method of manufacture of the bioadaptable material, but is also based on the conditions under which the biomaterial is incorporated into the bioadaptable material. A lower pressure environment, such that used in the present application, will give rise to adsorption. However, examples of conditions which give rise to non-adsorption include: (i) a high-pressure environment, (ii) immobilization (cross-linking) of genes to the implant by UV irradiation, and (iii) mixing bioadaptable filling such as collagen gel and alginate with genes to make an implant (See pages 9-10 of Applicant's remark filed on 10/14/2008).

Applicant argues that the pending claims are apparatus claims, not method claims or product-by-process claims. As such, it is not necessary to recite specific conditions. The claims read on an implant having Runx2 adsorbed onto a bioadaptable material, regardless of how this adsorption occurred. Applicants' previous remarks were merely illustrative of the point that a nucleic acid may or may not be adsorbed on an implant, depending in part on the conditions of

incorporation. As such, it is improper to presume that any reference which cites Runx2 and bioadaptable materials, such as Doll, anticipates the claim (See page 10 of Applicant's remark filed on 10/14/2008)

Applicant summarizes the arguments as follows:

1. Ogawa does not disclose adsorption of nucleic acids on to a bioadaptable material, but rather only discloses adsorption of acidic proteins onto a bioadaptable material.
2. Ogawa discloses that the ability of a bioadaptable material to adsorb acidic proteins depends upon the method of manufacture of the bioadaptable material. Even if Ogawa disclosed or suggested adsorption of nucleic acids onto a bioadaptable material, it can be presumed that such adsorption would also depend on the method of manufacture of the bioadaptable material.
3. The ability of a bioadaptable material to adsorb nucleic acids also depends upon the conditions of incorporation.

Applicants concludes that Doll does not inherently or explicitly disclose a bioadaptable porous material on which nucleic acids are adsorbed, and that adsorption of biomaterials, such as nucleic acids and acidic proteins, is not an inherent feature of a biodeadaptable porous material.

Response to Applicant's arguments

The Examiner agrees with Applicant in term of the claims as written are not product product-by-process claims. However, Applicant's arguments are centered on the conditions how the claimed bioadaptable porous materials selected from the group consisting hydroxypapatite,

α-TCP (α-tricalcium phosphate), β-TCP, collagen, polylactic acid, hyaluronic acid, polyglycolic acid, and a complex of any thereof, are manufactured, and the conditions how nucleic acid are incorporated into the claimed bioadaptable porous materials. Accordingly, the essence of Applicant's arguments are that the claimed products are patentably distinct from the products disclosed in the cited prior art because the process for making the claimed products are different. In this regard, Applicant is reminded that the claims as written are broad as the claims only recite hydroxypapatite, α-TCP (α-tricalcium phosphate), β-TCP etc as bioadaptable porous materials, and there is no recitation of any structural characteristics of the claimed hydroxypapatite, α-TCP (α-tricalcium phosphate), β-TCP. The structural characteristics include porosity (i.e. pore size and density) of claimed hydroxyapatite, α-TCP (α-tricalcium phosphate), β-TCP and variations in the characteristics have been disclosed in Ogawa et al. (US patent 5,030,611, issued 07/09/1991). Therefore, in the absence of recitation of any structural characteristics of claimed hydroxyapatite, α-TCP (α-tricalcium phosphate), β-TCP etc, the Examiner maintains the position that claims 9-12 and 14-23 as being anticipated by Doll et al. as evidenced by Ogawa et al. because the hydroxyapatite and β-TCP (β-tricalcium phosphate) disclosed in the cited references can absorb nucleic acid as the claimed hydroxyapatite and β-TCP (β-tricalcium phosphate) can, regardless the presence of possible variations in efficiency/efficacy of absorption of nucleic acid due to different processes how these bioadaptable porous materials being manufactured and conditions how nucleic acid being incorporated, as Applicant argues. The following citations, as documented in the maintained rejection, further clarify this point.

"Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an

applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product (In re Ludtke). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972))."

"When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433. See also Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), In re Ludtke, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), Northam Warren Corp. v. D. F. Newfield Co., 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934.) See MPEP 2113 and MPEP 2112.01.
Even though product-by-process claims are limited by and defined by the process; determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

"The Patent Office bears a lesser burden of proof in making out a case of prima facie obviousness for product-by-process claims because of their peculiar nature" than when a product is claimed in the conventional fashion. In re Fessmann, 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983).

Conclusion

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

4. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30

PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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